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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

EXAMINER	
STOCKTON, LAURA LYNNE	
ART UNIT	PAPER NUMBER
1626	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,622	JARVINEN ET AL.	
	Examiner	Art Unit	
	Laura L. Stockton	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4 and 7-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4 and 7-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 4 and 7-10 are pending in the application.

Response to Amendment

This Office Action supersedes the Office Action mailed March 18, 2009. The finality of the Office Action of June 11, 2008 is hereby withdrawn. The Amendment filed October 10, 2008 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4 and 7-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutically acceptable salt of the compound in the instant claims, does not reasonably provide enablement for a hydrate of the

compound in the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in making an enablement rejection are summarized as:

a) the quantity of experimentation necessary,

b) the amount of direction or guidance presented,

c) the presence or absence of working examples,

d) the nature of the invention,

e) the state of the prior art,

f) the relative skill of those in the art,

g) the predictability or unpredictability of the art, and

h) the breadth of the claims.

In re Colianni, 195 USPQ 150 (CCPA 1977). *In re Rainer*, et al., 146 USPQ 218 (CCPA 1965). *Ex parte Formal*, 230 USPQ 546 (BPAI 1986).

a) Determining if a particular compound would form a hydrate would require synthesis and recrystallization of the compound using a variety of temperatures and humidities. The experimentation for hydrates is potentially open-ended.

b) The specification merely mentions the Applicant's intention to make hydrates, without teaching the preparation thereof.

c) While the claims recite hydrates, no working examples show their formation. As stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190, 1194 (Fed.Cir. 1993):

> The specification purports to teach, with over fifty examples, the preparation of the claimed compounds ... However ... there is no evidence that such compounds exist ... [T]he examples ... do not produce the postulated compounds ... [T]here is ... no evidence that such compounds even exist.

The specification shows no evidence of the formation and actual existence of hydrates. Hence,

Applicant must show formation of hydrates or limit the claims accordingly.

d) The nature of the invention is chemical synthesis of hydrates, which involves chemical reactions.

e) The state of the art recognizes that the formation, composition and therapeutic activity of hydrates is unpredictable. The Federal Circuit has recognized a solvate as an example of a polymorph or pseudopolymorph (emphasis added):

> "Polymorphs" are distinct crystalline structures containing the same molecules. These structural differences can affect various properties of the crystals, such as melting points and hardness (e.g., graphite and diamonds are both crystalline forms of carbon) .... [P]seudopolymorphs are often loosely called polymorphs ... Pseudopolymorphs not only have their molecules arranged differently but also have a slightly different molecular composition. A common type of pseudopolymorph is a solvate, which is a crystal in which the molecules defining the crystal structure "trap" molecules of a solvent. The crystal molecules and the solvent molecules then bond to form an altered crystalline structure.

SmithKline Beecham Corp. v. Apotex Corp., 74 USPQ2d 1398, 1409 (Fed.Cir. 2005). The same rationale obtains for hydrates; solvates in which the solvent is water. Souillac, et al., Characterization of Delivery Systems, Differential Scanning Calorimetry, pages 217-218 (in Encyclopedia of Controlled Drug Delivery, 1999, John Wiley & Sons, pages 212-227), recognize that different polymorphs of the same drug can have different therapeutic activity (emphasis added):

> Because different polymorphic forms of the same drug exhibit significant differences in their physical characteristics, therapeutic activity from one form to another may be different. Studying the polymorphism of a drug and the relative stability of the different polymorphs is a critical part of pre-formulation development.

Further, Vippagunta et al. (Advanced Drug Delivery Reviews, 48 (2001), pages 3-26) state "Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated in to the crystal lattice of a compound is complex and difficult." See page 18, section 3.4.

f) The artisan using Applicant's disclosure to prepare the claimed hydrates would be, e.g., an experienced process chemist with at least a BS chemistry degree.

g) Chemical reactions are known as unpredictable. *In re Marzocchi, et al.*, 169 USPQ 367, 370 (CCPA 1971); *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). See above regarding the unpredictability of hydrate formation.

h) The breadth of the claims includes a compound in the instant claims as well as presently unknown compounds embraced by the term hydrates. See MPEP 2164.01(a), discussed supra, justifying the conclusion of lack of enablement commensurate with the claims. Undue experimentation will be required to practice Applicant's claimed invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as

to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 4 and 7-10 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5, 6, 8, 14 and 16-24 of U.S. Patent No. 6,313,311. Although the conflicting

claims are not identical, they are not patentably distinct from each other because the instant claimed compound is generically described in the patent.

The indiscriminate selection of "some" among "many" is *prima facie* obvious, *In re Lemin*, 141 USPQ 814 (1964). The motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity (e.g., treating hypertension).

One skilled in the art would thus be motivated to prepare products embraced by the patent to arrive at the instant claimed products with the expectation of obtaining additional beneficial products which would be useful in treating, for example, hypertension. The instant claimed invention would have been suggested to one skilled in the art and therefore, the instant claimed invention would have been obvious to one skilled in the art.

Claims 7 and 8 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 15, 16, 19-24 and 27-32 of copending Application No. 11/641,953 {US 2007/0185181}. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application claims methods of using imidazole compounds which generically embrace the imidazole compound being used in the instant claimed method of use.

The indiscriminate selection of "some" among "many" is *prima facie* obvious, *In re Lemin*, 141 USPQ 814 (1964). The motivation to make the compounds for the instant claimed methods of use derives from the expectation that structurally similar compounds would possess similar activity (e.g., treating hypotension).

One skilled in the art would thus be motivated to prepare products embraced by the copending application to arrive at the instant products for the instant

claimed method of use with the expectation of obtaining additional beneficial products which would be useful in treating, for example, hypotension. The instant claimed invention would have been suggested to one skilled in the art and therefore, the instant claimed invention would have been obvious to one skilled in the art.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's arguments with respect to claims 1, 4 and 7-10 under 35 USC 103 over Karjalainen et al. {WO 97/12874}, taken alone, or Karjalainen et al. in view of Huhtala et al. {WO 01/051472} have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4 and 7-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Karjalainen et al. {WO 97/12874} and Karjalainen et al. {U.S. Pat. 6,313,311}, each taken alone, or each of the aforementioned Karjalainen et al. references in view of Huhtala et al. {WO 01/051472}, Bundgaard {**No. 1 -** Drugs of the Future, 1991, 16(5), pages 443-458}, Aungst et al. {U.S. Pat. 4,673,679} and Bundgaard {**No. 2** – A Textbook of Drug Design and Development, Harwood Academic Publishers, 1991, Chapter 5, pages 113-191}.

Determination of the scope and content of the prior art (MPEP §2141.01)

Applicant claims imidazole compounds. Karjalainen et al. '874 (see entire document; particularly pages 1-4, 11 and 12; and especially Example 15 on page 30) and Karjalainen et al. '311 (see entire document; particularly columns 1-3, 10 and 11; and especially Example 15 in column 21) each teach imidazole compounds that are structurally similar to the instant claimed compounds.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between the compounds of the Karjalainen et al. references and the compound instantly claimed is that the instant claimed compound is generically described, and claimed, in each of the Karjalainen et al. references as a pharmaceutically acceptable ester.

Huhtala et al. (page 8, last full paragraph) teach the interchangeability of esters of aliphatic and aromatic alcohols {i.e., the -C(=O)R group in instant

formula (I)}. Huhtala et al. state that the -OH functionality forms esters with pharmaceutically acceptable acids which are conventional in the field of pharmaceuticals and retain the pharmacological properties of the free form.

Bundgaard (**No. 1**) teaches the advantages of ester prodrugs and why one skilled in the art would be motivated to prepare such ester prodrugs (see entire document; particularly page 444, first column, first full paragraph through to the second column under "Ester prodrugs"). Aungst et al. (column 1, lines 40-48; column 3, lines 1-20; and column 5, lines 20-27, 35-55 and 65-67) and Bundgaard (**No. 2** - see the reverse process in Scheme 5.13 at the at the top of page 151; page 153; Table 5.5 on page 154; and page 156) each teach the preparation of a prodrug from a hydroxy containing active ingredient using the process taught in Huhtala et al. of the -OH functionality reacting with a pharmaceutically acceptable acid.

Finding of prima facie obviousness--rational and motivation (MPEP §2142-2413)

The indiscriminate selection of "some" among "many" is *prima facie* obvious, *In re Lemin*, 141 USPQ 814 (1964). The motivation to make the claimed compounds of the Karjalainen et al. references derives from the expectation that structurally similar compounds would possess similar activity (e.g., treating glaucoma).

One skilled in the art would thus be motivated to prepare products embraced by the Karjalainen et al. references, especially in view of the teachings in Huhtala et al., Bundgaard (**No. 1**), Aungst et al. and Bundgaard (**No. 2**), to arrive at the instant claimed products with the expectation of obtaining additional beneficial products which would be useful in treating, for example, glaucoma, psychiatric and cognition disorders, etc. The instant claimed invention would have been suggested to one skilled in the art and therefore, the instant claimed invention would have been obvious to one skilled in the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura L. Stockton whose telephone number is (571) 272-0710. The examiner can normally be reached on Monday-Friday from 6:15 am to 2:45 pm. If the examiner is out of the Office, the examiner's supervisor, Joseph McKane, can be reached on (571) 272-0699.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

The Official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

/Laura L. Stockton/
Laura L. Stockton
Patent Examiner
Art Unit 1626, Group 1620
Technology Center 1600

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